

IN THE CLAIMS:

1. (Currently amended) A composition comprising at least one salt chosen from alkali and ~~or~~ alkaline-earth metal salts of at least one sulphated polysaccharide of heparin, said ~~at least one alkali or alkaline-earth metal salts~~ of at least one sulphated polysaccharide of heparin ~~having~~ comprising:

a mean molecular weight in the range of 1500 to 3000 daltons;

an anti-Xa activity in the range of 110 ~~425~~ to 150 IU/mg;

an anti-IIa activity in the range of up to 10 IU/mg; and

an anti-Xa activity/anti-IIa activity ratio greater than 10:1.

2. (Currently amended) A composition comprising at least one salt chosen from alkali and ~~or~~ alkaline-earth metal salts of at least one sulphated polysaccharide of heparin, in which ~~the alkali or alkaline-earth metal~~ said salts of at least one sulphated polysaccharide of heparin have ~~has~~ 2 to 26 saccharide units, have an anti-Xa activity in the range of 110 ~~425~~ to 150 IU/mg, have a mean molecular weight in the range of 1500 to 3000 daltons, and have ~~has~~ a 4,5-unsaturated glucuronic acid 2-O-sulphate unit at on at least one end.

3. (Cancelled)

4. (Cancelled)

5. (Currently amended) A composition according to claim 1 ~~2~~ having a mean molecular weight in the range of 2000 to 3000 daltons.

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6. (Currently amended) A composition according to claim 1 2 having anti-Xa activity in the range of 140 to 150 IU/mg and a mean molecular weight in the range of 2000 to 3000 daltons.
7. (Currently amended) A composition according to claim 1 2, in which ~~the at least one alkaline-earth metal~~ said salts are chosen from ~~is a~~ sodium, potassium, calcium, and ~~or~~ magnesium salts.
8. (Currently amended) A composition according to claim 1 2, having an anti-IIa activity ~~in the range of~~ up to 5 IU/mg.
9. (Original) A composition according to claim 1 2, having an anti-Xa activity:anti-IIa activity ratio greater than 25.
10. (Currently amended) ~~The~~ A method of preparing at least one salt chosen from alkali ~~or~~ and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin comprising:

depolymerizing a at least one quarternary ammonium salt of the benzyl ester of heparin in an organic medium with ~~a base with a pKa greater than 20;~~ at least one phosphazene base;

converting the at least one quarternary ammonium salt of the benzyl ester of the depolymerized heparin to a at least one sodium salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin;

saponifying the at least one salt ester; and

optionally purifying the at least one salt product.

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~~wherein said base is 1,5,7 triazabicyclo [4.4.0] dec 5 ene, 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diaza-phosphorine, a guanidine base, or a phosphazene base.~~

11. (Currently amended) The method according to claim 10, in which ~~the at least one alkaline-earth metal~~ said salts of at least one sulphated polysaccharide of heparin ~~have~~ has a mean molecular weight in the range of 1500 to 3000 daltons.

12. (Currently amended) The method according to claim 10, in which ~~the at least one alkaline-earth metal~~ said salts of at least one sulphated polysaccharide of heparin ~~have~~ has an anti-Xa activity in the range of 94 to 150 IU/mg.

13. (Currently amended) The method according to claim 10, in which ~~the at least one alkaline-earth metal~~ said salts of at least one sulphated polysaccharide of heparin ~~have~~ has an anti-IIa activity ~~in the range of~~ up to 10 IU/mg.

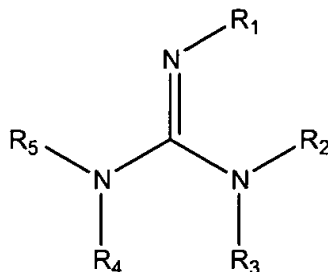
14. (Currently amended) The method according to claim 10, in which ~~the at least one alkaline-earth metal~~ said salts of at least one sulphated polysaccharide of heparin ~~have~~ has an anti-Xa activity:anti-IIa activity ratio greater than 10:1.

15. (Currently amended) The method according to claim 10, in which ~~the at least one alkaline-earth metal~~ said salts of at least one sulphated polysaccharide of heparin ~~comprises~~ have 2 to 26 saccharide units and have ~~has~~ a 4,5-unsaturated glucuronic acid 2-O-sulphate unit ~~at on~~ at least one end.

16. (Currently amended) The method according to claim 10, in which the ~~quaternary~~ quarternary ammonium salt of the benzyl ester of heparin is a chosen from benzethonium, cetylpyridinium, ~~or~~ and cetyltrimethylammonium salts.

17. (Cancelled)

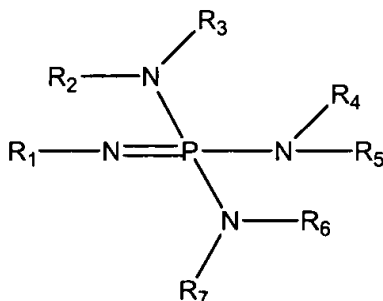
18. (Currently amended) The method according to claim 10 ~~40~~ 61, in which the at least one base of guanidine comprises:



where R₁ is chosen from hydrogen or and alkyl, and where R₂, R₃, R₄, and R₅, which are identical or different, are and each chosen from ~~is a~~ C₁-C₆ alkyl.

19. (Original) The method according to claim 18, where R₁ is hydrogen, and R₂, R₃, R₄, and R₅ are each methyl.

20. (Currently amended) The method according to claim 10, in which the at least one phosphazene base ~~of phosphazene comprises~~ is chosen from:



where R₁ to R₇ are identical or different, and are each chosen from ~~is a~~ C₁-C₆ alkyl.

21. (Currently amended) The method according to claim 10, in which the mol ratio of the at least one phosphazene base ~~with a pKa greater than 20~~ to the at least one quarternary ~~quaternary~~ ammonium salt of the benzyl ester of heparin ranges from 0.2:1 to 5:1.

22. (Currently amended) The method according to claim 10, in which ~~the degree of esterification of the~~ said at least one quarternary quaternary ammonium salt of the benzyl ester of heparin ~~ranges~~ has a degree of esterification ranging from 50 to 100%.

23. (Currently amended) The method according to claim 10, in which the at least one quarternary quaternary ammonium salt of the benzyl ester of depolymerized heparin is converted to a sodium salt by treating the reaction medium with an alcoholic solution of sodium acetate.

24. (Original) The method according to claim 10, in which the saponification is carried out by an alkali metal hydroxide.

25. (Original) The method according to claim 10, in which the purification is carried out by hydrogen peroxide.

26. (Currently amended) ~~The~~ A method of preparing at least one salt chosen from alkali and ~~or~~ alkaline-earth metal salts of at least one sulphated polysaccharide of heparin comprising:

depolymerizing a at least one quarternary quaternary ammonium salt of the benzyl ester of heparin in an organic medium with sodium imidazolate;

converting the at least one quarternary quaternary ammonium salt of the benzyl ester of the depolymerized heparin to a ~~sodium~~ at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin;

saponifying the at least one salt ester; and

optionally purifying the at least one salt product.

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27. (Currently amended) The method according to claim 26, in which ~~the at least one alkali or alkaline earth metal~~ said salts of at least one sulphated polysaccharide of heparin ~~has~~ have a mean molecular weight in the range from 1500 to 3000 daltons.
28. (Currently amended) The method according to claim 26, in which ~~the at least one alkali or alkaline earth metal~~ said salts of at least one sulphated polysaccharide of heparin ~~has~~ have an anti-Xa activity in the range from 94 to 150 IU/mg.
29. (Currently amended) The method according to claim 26, in which ~~the at least one alkali or alkaline earth metal~~ said salts of at least one sulphated polysaccharide of heparin ~~has~~ have an anti-IIa activity ~~in the range of~~ up to 10 IU/mg.
30. (Currently amended) The method according to claim 26, in which ~~the at least one alkali or alkaline earth metal~~ said salts of at least one sulphated polysaccharide of heparin ~~has~~ have an anti-Xa activity:anti-IIa activity ratio greater than 10:1.
31. (Currently amended) The method according to claim 26, in which ~~the at least one alkali or alkaline earth metal~~ said salts of at least one sulphated polysaccharide of heparin ~~comprises~~ have 2 to 26 saccharide units and ~~has~~ have a 4,5-unsaturated glucuronic acid 2-O-sulphate unit ~~at on~~ at least one end.
32. (Currently amended) The method according to claim 26, in which the at least one quarternary quaternary ammonium salt of the benzyl ester of heparin is chosen from a benzethonium, cetylpyridinium, and ~~or~~ cetyltrimethylammonium salts.
33. (Currently amended) The method according to claim 26, in which the mol ratio of the sodium imidazolate to the at least one quarternary quaternary ammonium salt of the benzyl ester of heparin ranges from 0.2:1 to 5:1.

34. (Currently amended) The method according to claim 26, in which ~~the degree of esterification of the~~ said at least one quarternary quaternary ammonium salt of the benzyl ester of heparin ~~ranges~~ has a degree of esterification ranging from 50 to 100%.

35. (Currently amended) The method according to claim 26, in which the at least one quarternary quaternary ammonium salt of the benzyl ester of depolymerized heparin is converted to a sodium salt by treating the reaction medium with an alcoholic solution of sodium acetate.

36. (Original) The method according to claim 26, in which the saponification is carried out by an alkali metal hydroxide.

37. (Original) The method according to claim 26, in which the purification is carried out by hydrogen peroxide.

38. (Original) A method of treating venous thrombosis in a patient in need of such treatment, comprising administering to the patient a composition as claimed in claim 2, in an amount efficacious for the treatment of venous thrombosis.

39. (Currently amended) A method of treating venous thrombosis in a patient in need of such treatment, comprising administering to the patient a composition ~~prepared according to the method~~ as claimed in claim 1 ~~40~~, in an amount efficacious for the treatment of venous thrombosis.

40. (Currently amended) A method of treating venous thrombosis in a patient in need of such treatment, comprising administering to the patient a composition ~~prepared according to the method~~ as claimed in claim 57 ~~26~~, in an amount efficacious for the treatment of venous thrombosis.

41. (Currently amended) A method of treating arterial ~~thrombotic accidents~~ thrombosis in a patient in need of such treatment, comprising administering to the patient a composition as claimed in claim 2, in an amount efficacious for the treatment of arterial ~~thrombotic accidents~~ thrombosis.

42. (Currently amended) A method of treating arterial ~~thrombotic accidents~~ thrombosis in a patient in need of such treatment, comprising administering to the patient a composition ~~prepared according to the method~~ as claimed in claim 1 ~~40~~, in an amount efficacious for the treatment of arterial ~~thrombotic accidents~~ thrombosis.

43. (Currently amended) A method of treating arterial ~~thrombotic accidents~~ thrombosis in a patient in need of such treatment, comprising administering to the patient a composition ~~prepared according to the method~~ as claimed in claim 57 ~~26~~, in an amount efficacious for the treatment of arterial ~~thrombotic accidents~~ thrombosis.

44. (Currently amended) A method of treating arterial ~~thrombotic accidents~~ or venous thrombosis in a patient in need of such treatment comprising the administration of a solution of a pharmaceutical composition by the subcutaneous, intramuscular, intravenous, or pulmonary route, in which a composition according to claim 2 is an active ingredient present in an amount efficacious for such treatment.

45. (Currently amended) A method of treating arterial ~~thrombotic accidents~~ or venous thrombosis in a patient in need of such treatment comprising the administration of a solution of a pharmaceutical composition by the subcutaneous, intramuscular, intravenous, or pulmonary route, in which a composition ~~produced by the method~~ according to claim 1 ~~40~~ is an active ingredient present in an amount efficacious for such treatment.

46. (Currently amended) A method of treating arterial ~~thrombotic accidents~~ or venous thrombosis in a patient in need of such treatment comprising the administration of a solution of a pharmaceutical composition by the subcutaneous, intramuscular, intravenous, or pulmonary route, in which a composition ~~produced by the method~~ according to claim 57 26 is an active ingredient present in an amount efficacious for such treatment.

47. through 55. (Cancelled)

56. (New) A composition comprising at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin, wherein said salt is prepared according to the method of claim 10.

57. (New) A composition according to claim 2 having anti-Xa activity in the range of 125-150 IU/mg.

58. (New) A composition according to claim 1, in which said at least one salt is sodium salt.

59. (New) A method of preparing at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin comprising:

depolymerizing at least one quarternary ammonium salt of the benzyl ester of heparin in an organic medium with 1,5,7 triazabicyclo-[4.4.0]-dec-5-ene;

converting the at least one quarternary ammonium salt of the benzyl ester of the depolymerized heparin to at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin;

saponifying the at least one salt; and

optionally purifying the at least one salt.

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60. (New) The method according to claim 10, wherein said at least one phosphazene base is 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diaza-phosphorine.

61. (New) A method of preparing at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin comprising:

depolymerizing at least one quarternary ammonium salt of the benzyl ester of heparin in an organic medium with at least one guanidine base;

converting the at least one quarternary ammonium salt of the benzyl ester of the depolymerized heparin to at least one salt chosen from alkali and alkaline-earth metal salts of at least one sulphated polysaccharide of heparin;

saponifying the at least one salt; and

optionally purifying the at least one salt.

62. (New) A method of preparing a composition comprising the sodium salt of at least one sulphated polysaccharide of heparin, said sodium salt of at least one sulphated polysaccharide of heparin comprising:

a mean molecular weight in the range of 1500 to 3000 daltons;

an anti-Xa activity in the range of 94 to 150 IU/mg;

an anti-IIa activity in the range of up to 10 IU/mg; and

an anti-Xa activity/anti-IIa activity ratio greater than 10:1

wherein said method comprises:

depolymerizing a quarternary ammonium salt of the benzyl ester of heparin in an organic medium with a phosphazene base;

converting the quarternary ammonium salt of the benzyl ester of the depolymerized heparin to a sodium salt of at least one sulphated polysaccharide of heparin;

saponifying the sodium salt; and

optionally purifying the sodium salt.

63. (New) The method according to claim 62, in which said sodium salt of at least one sulphated polysaccharide of heparin have an anti-Xa activity in the range of 110 to 150 IU/mg.

64. (New) A method of preparing a composition comprising the sodium salt of at least one sulphated polysaccharide of heparin, said sodium salt of at least one sulphated polysaccharide of heparin comprising:

a mean molecular weight in the range of 1500 to 3000 daltons;

an anti-Xa activity in the range of 94 to 150 IU/mg;

an anti-IIa activity in the range of up to 10 IU/mg; and

an anti-Xa activity/anti-IIa activity ratio greater than 10:1

wherein said method comprises:

depolymerizing a quarternary ammonium salt of the benzyl ester of heparin in an organic medium with 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine;

converting the quarternary ammonium salt of the benzyl ester of the depolymerized heparin to a sodium salt of at least one sulphated polysaccharide of heparin;

saponifying the sodium salt; and

optionally purifying the sodium salt.

65. (New) A method of preparing a composition comprising the sodium salt of at least one sulphated polysaccharide of heparin, said sodium salt of at least one sulphated polysaccharide of heparin comprising:

a mean molecular weight in the range of 1500 to 3000 daltons;

an anti-Xa activity in the range of 94 to 150 IU/mg;

an anti-IIa activity in the range of up to 10 IU/mg; and

an anti-Xa activity/anti-IIa activity ratio greater than 10:1

wherein said method comprises:

depolymerizing a quarternary ammonium salt of the benzyl ester of heparin in an organic medium with 1,5,7 triazabicyclo-[4.4.0]-dec-5-ene;

converting the quarternary ammonium salt of the benzyl ester of the depolymerized heparin to a sodium salt of at least one sulphated polysaccharide of heparin;

saponifying the sodium salt; and

optionally purifying the sodium salt.

66. (New) A method of preparing at least one salt chosen from alkali and alkaline-earth metal salts of sulphated polysaccharides of heparin comprising:

depolymerizing at least one quarternary ammonium salt of the benzyl ester of heparin in an organic medium with at least one base with a pKa greater than 20;

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converting the at least one quarternary ammonium salt of the benzyl ester of the depolymerized heparin to at least one salt chosen from alkali and alkaline-earth metal salts of sulphated polysaccharides of heparin;

saponifying the at least one salt; and

optionally purifying the at least one salt.

67. (New) A method of preparing a sodium salt of sulphated polysaccharides of heparin comprising:

depolymerizing a quarternary ammonium salt of the benzyl ester of heparin in an organic medium with at least one base with a pKa greater than 20;

converting the quarternary ammonium salt of the benzyl ester of the depolymerized heparin to the sodium salt of sulphated polysaccharides of heparin;

saponifying the sodium salt; and

optionally purifying the sodium salt.

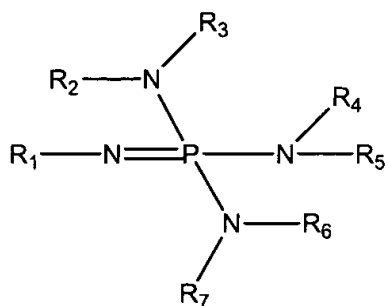
68. (New) The method according to claim 67, wherein said depolymerizing step is accomplished with a single base with a pKa greater than 20.

69. (New) The method according to claim 68, wherein said base is 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diaza-phosphorine.

70. (New) The method according to claim 10, in which the at least one phosphazene base is chosen from:

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where R₁ to R₇ are identical or different, and are each chosen from C₁-C₆ alkyl and, further where R₃ and R₄ or R₁ and R₇, taken together with the nitrogens to which they are attached, may form a saturated ring chosen from substituted and unsubstituted six member rings.

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